Age-Related Cognitive Decline: the Roles of Physical Activity and the Apolipoprotein E e4 Allele

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Statement of Sources

I declare that this report is my own original work and that contributions of others have been duly acknowledged.

Signed:

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Abstract

We examined the effects of physical activity and the apolipoprotein E e4 allele (APOEe4) on age-related cognitive decline amongst a sample of cognitively normal middle-aged and older adults. Forty-seven participants (76.6% female; 23.4% male) aged 50-71 at baseline (M = 60.0, SD = 5.8) wore an accelerometer to record total weekly level of physical activity. Participants also underwent APOE genotyping and annual cognitive tests assessing long-term memory and learning, working memory, and executive functioning through the Tasmanian Healthy Brain Project. We conducted a series of three-way mixed analyses of variance to test for interaction effects between physical activity status (active; inactive), APOEe4 status (carrier; non-carrier), and assessment phase (1; 2; 3; 4) on performance on each of the cognitive tests. For all cognitive tests, there were no consistent effects of physical activity, no consistent effects of APOEe4, and no significant interaction effects between physical activity, APOEe4, and phase of assessment. Findings suggest that physical activity, APOEe4, or combinations of the two do not influence non-pathological age-related cognitive decline. Future research would benefit from examining the possibility that APOEe4 may be detrimental to cognitive decline for individuals that carry two copies of the allele, and from examining whether lifetime levels of physical activity or specific types of physical activity influence age-related cognitive decline.

Keywords: ageing, long-term memory, working memory, executive functioning, gene-environment interaction

Growing old is associated with a gradual decline in cognitive function (Salthouse, 2009). This cognitive decline is typically characterised by subtle decreases in memory performance, speed of processing, and executive functioning and does not significantly impair daily functioning (Park et al., 2002; Park & Reuter-Lorenz, 2009). Although cognitive decline is a normal consequence of ageing, it can nonetheless be distressing for individuals and their families to experience. Normal age-related cognitive decline begins prior to the age of 60 years (Salthouse, 2009). As life expectancy is increasing and the worldwide population is ageing (World Health Organization, 2015), it is expected that the number of individuals experiencing age-related cognitive decline at any one time will increase over future years.

While most people experience cognitive decline as they age, some individuals decline at a faster rate than others. A pronounced rate of cognitive deterioration can be indicative of dementia, such as Alzheimer's disease, and is not part of the normal ageing process (McKhann et al., 2011). Past research into later-life cognition has largely focused on the effectiveness of treatment interventions in alleviating the pathogenic processes that are present in clinical and pre-clinical stages of Alzheimer's disease. However, these interventions have been largely unsuccessful (Brini et al., 2017). It is possible that this is because the interventions are administered during the symptomatic stages of Alzheimer's disease, at which point irreversible neural damage has already taken place (Sperling, Jack, & Aisen, 2011). Identifying factors that may influence the rate of age-related cognitive decline, prior to clinically significant cognitive impairment, may be more effective at reducing the burden of dementia and Alzheimer's disease. Additionally, it may be possible to identify preventative interventions which could benefit older adults who wish to

delay or slow normal age-related cognitive decline, not only those at increased risk of dementia.

Two factors that may influence the rate of age-related cognitive decline are physical activity and the epsilon 4 (e4) allele of the apolipoprotein E gene (APOE). Physical activity refers to "any bodily movement produced by skeletal muscles that results in energy expenditure" (Caspersen, Powell, & Christenson, 1985, p. 126), and has been recognised as a modifiable behaviour that mitigates age-related cognitive decline (Sofi et al., 2010). In contrast, the e4 allele of the APOE gene has been associated with an increased rate of cognitive decline in normal ageing (Small, Rosnick, Fratiglioni, & Bäckman, 2004). While an individual cannot change their genetic status, it is possible that physical activity may interact with the influence of APOEe4 on age-related cognitive decline. An understanding of whether physical activity interacts with APOEe4 could help to develop potential interventions to delay or slow age-related cognitive decline.

Physical Activity and Cognitive Decline

Physical activity is known to improve and maintain neurocognitive health (Stillman, Cohen, Lehman, & Erickson, 2016). Prospective cohort studies have shown that cognitively normal older adults who engage in regular physical activity experience less decline in the cognitive domains of executive functioning and processing speed, as well as general cognitive performance (Best et al., 2017; Frederiksen et al., 2015; Sofi et al., 2010). Additionally, those who are physically active are less likely to be cognitively impaired or be diagnosed with Alzheimer's disease, compared to those who are inactive (Barnes et al., 2008; Buchman et al., 2012; Wang et al., 2013). The protective effects of physical activity on cognitive

decline seem to be greatest at high levels of physical activity, but are also significant at low and moderate levels (Sofi et al., 2010).

Several possible mechanisms for the protective effect of physical activity on cognitive function have been suggested. Firstly, physical activity increases blood levels of brain-derived neurotrophic factor, insulin-like growth factor-1, and vascular endothelial-derived growth factor. In turn, combinations of these growth factors regulate neuroplasticity, neurogenesis and cerebrovascular perfusion, all of which are imperative to cognitive function (Cotman, Berchtold, & Christie, 2007; Stillman et al., 2016). Furthermore, physical activity is known to reduce peripheral risk factors for cognitive decline, including systemic inflammation, hypertension, hyperglycaemia, and dyslipidaemia (Cotman et al., 2007; Stillman et al., 2016). Finally, physical activity is also thought to indirectly benefit cognition through its beneficial influence on stress, mood, and sleep (Cotman et al., 2007; Sofi et al., 2010; Stillman et al., 2016).

The APOE Gene and Cognitive Decline

Past research suggests that physical activity is beneficial in mitigating age-related cognitive decline. However, even when accounting for level of physical activity, inter-individual differences remain. It is possible that genetic factors account for some of these inter-individual differences. One genetic factor that influences cognitive decline is the APOE gene (Small et al., 2004).

The APOE gene synthesises apolipoprotein E (ApoE), which is a plasma protein (Small et al., 2004). The main functions of ApoE include lipid transport, cholesterol metabolism, and processes involved in neuronal repair (Liu, Kanekiyo, Xu, & Bu, 2013; Phillips, 2014; Small et al., 2004). There are three main allelic variations of the APOE gene, e2, e3, and e4, and each allele provides the genetic

information for a different isoform of ApoE (Phillips, 2014). Individuals inherit one allele from each parent, allowing for six possible genotypes, e2/e2; e2/e3; e2/e4; e3/e3; e3/e4; e4/e4 (Small et al., 2004). The e3 allele is the most common allele amongst the worldwide population with a frequency of 72%, followed by e4 (17%) and e2 (11%; Zannis, Kardassis, & Zannis, 1993).

The e4 allele of the APOE gene is recognised as a risk factor for pathological cognitive decline, with it known as the primary genetic risk factor for Alzheimer's disease (Harold et al., 2009; Lindsay et al., 2002). Individuals who carry one copy of APOEe4 are at a 3-4 times increased risk of Alzheimer's disease, while individuals who carry two copies of the e4 allele are at a 10-12 times increased risk of Alzheimer's disease, compared to those who do not carry APOEe4 (Farrer et al., 1997). Additionally, amongst individuals with a diagnosis of Alzheimer's disease, APOEe4 carriers typically show an earlier onset (Corder et al., 1993; Farrer et al., 1997), and a faster rate of cognitive decline (Martins, Oulhaj, de Jager, & Williams, 2005), compared to non-carriers.

Moreover, research suggests that the presence of APOEe4 has a detrimental effect on cognitive decline in normal ageing (Small et al., 2004; Wisdom, Callahan, & Hawkins, 2011). Those who carry APOEe4 are more likely to experience multiple-domain decline, despite retaining a normal clinical status, than those who do not carry APOEe4 (Caselli et al., 2007). Healthy APOEe4 carriers typically show an increased rate of age-related decline across several domains of cognition, including verbal memory, episodic memory and executive function, as well as global cognitive functioning (Caselli et al., 2004; Caselli et al., 2007; Small et al., 2004). The increased rate of memory decline for APOEe4 carriers becomes apparent prior to the age of 60 years (Caselli et al., 2009). Taken together, these findings suggest that

APOEe4 has a detrimental influence on normal age-related cognitive decline. However this finding is not consistent, with some studies showing no independent effect of the e4 allele on cognition amongst healthy older adults (Foster et al., 2013; Ward et al., 2014; Quintas et al., 2014).

Several possible mechanisms for the potentially detrimental influence of APOEe4 on cognitive decline have been suggested. Firstly, cognitively normal individuals who carry APOEe4 show reduced cerebrospinal fluid amyloid beta 42 and increased cortical binding potential for Pittsburgh Compound-B, which together reflect increased cerebral amyloid beta deposition (Morris et al., 2010; Wirth, Villeneuve, La Joie, Marks, & Jagust, 2014). This amyloid beta deposition is thought to contribute to cognitive decline (Jack et al., 2010). Additionally, cognitively normal APOEe4 carriers show reduced rates of cerebral glucose metabolism (Reiman et al., 2004; Reiman et al., 2005; Small et al., 2000) and reduced grey matter volume and cortical thickness (Burggren et al., 2008; Fennema-Notestine et al., 2011), each of which are associated with cognitive decline.

The Interaction Between Physical Activity and APOEe4

Physical activity and APOEe4 have each been shown to influence age-related cognitive decline, however the interaction between these factors is unclear. In terms of overall cognitive functioning, a study by Obisesan, Umar, Paluvi, and Gillum (2012) found that being physically active, relative to being sedentary, was associated with better cognitive performance amongst healthy adults aged 60-69 years, but only for non-APOEe4 carriers. There was no association between physical activity and cognitive function amongst APOEe4 carriers. Relatedly, Podewils et al. (2005) found an inverse relationship between physical activity level and dementia risk amongst men and women aged 65 years and older, but this relationship was absent in APOEe4

carriers. Similarly, two studies conducted by Tolppanen et al. (2015) and Kulmala et al. (2014) found that higher levels of physical activity during midlife were associated with a lower risk of dementia diagnosis in later life, and this benefit was more pronounced amongst non-APOEe4 carriers, compared to APOEe4 carriers.

These findings suggest that the beneficial effects of physical activity are not strong enough to overcome the potentially detrimental influence of APOEe4 on cognition. However, all of these studies used the Mini-Mental State Examination (MMSE) to measure cognitive decline. The MMSE is a brief questionnaire that assesses global cognitive functioning and is not sensitive to performance differences between specific domains of cognition (Magni, Binetti, Bianchetti, Rozzini, & Trabucchi, 1996). However, some cognitive domains appear to be influenced more by physical activity and APOEe4 than others. Specifically, physical activity appears to have the greatest influence on executive function and processing speed in the absence of APOE grouping (Netz, Dwolatzky, Zinker, Argov, & Agmon, 2011; Wilbur et al., 2012), while APOEe4 appears to have a greater influence on executive function and episodic memory compared to other cognitive domains (Small et al., 2004). Thus, it is possible that studies examining the effects of physical activity and APOEe4 on domain-specific cognitive decline have a different pattern of results.

Indeed, a prospective cohort study of cognitively normal adults aged 45 years and older conducted by Pizzie et al. (2014) found that higher baseline physical activity was associated with small improvements in executive functioning and working memory performance over the subsequent four years, but only amongst APOEe4 carriers. There was no association between physical activity and decline trajectories of cognitive performance for non-APOEe4 carriers. Similar findings were reported by Thibeau, McFall, Camicioli, and Dixon (2017) who found that

lower physical activity levels were significantly associated with poorer baseline executive functioning and a more rapid decline in executive functioning amongst middle aged and older adults, but only for APOEe4 carriers. Finally, Etnier et al. (2007) found that greater levels of aerobic fitness were associated with better short-term, long-term, and working memory performance amongst middle aged and older women, but this association was only significant for those who carried two copies of APOEe4.

This pattern of results has also been found in some studies assessing global cognitive functioning. For example, Woodward et al. (2012) found that physical activity reduced the risk of cognitive decline amongst healthy older adults, but only for APOEe4 carriers. Furthermore, Niti, Yap, Kua, Tan, and Ng (2008) found that higher levels of physical activity were associated with lower odds of cognitive decline amongst healthy adults aged 55 years and older, and that this association was stronger for APOEe4 carriers, compared to non-APOEe4 carriers. Similarly, Schuit, Feskens, Launer, and Kromhout (2001) found that elderly men who engage in more than one hour of physical activity per day had lower odds of cognitive decline than those who engage in less than one hour of activity. Again, this difference was greater for APOEe4 carriers, compared to non-APOEe4 carriers. Finally, greater levels of physical activity have been associated with reduced odds of dementia and Alzheimer's disease, and these associations are more evident amongst APOEe4 carriers, compared to non-APOEe4 carriers (Luck et al., 2014; Kivipelto et al., 2008; Rovio et al., 2005; Tan et al., 2017; Yang et al., 2015).

The Scaffolding Theory of Ageing and Cognition

These findings suggest that physical activity is protective of later-life cognition, and the benefits are particularly pronounced for individuals who carry the

e4 allele of the APOE gene. One explanation of these findings is the Scaffolding Theory of Ageing and Cognition. This theory suggests that compensatory brain processes take place in order to maintain normal cognitive function in later life, despite the accumulation of ageing-related brain changes (Park & Reuter-Lorenz, 2009). These compensatory processes, often broadly referred to as neural scaffolding, may involve the engagement of increased neural circuitry and greater activation or recruitment of brain regions (Reuter-Lorenz & Park, 2014).

In accordance with this theory, research has found that cognitively healthy individuals who carry the APOEe4 allele typically exhibit increased task-related activity in multiple brain areas compared to their non-APOEe4 carrier counterparts (Bookheimer et al., 2000; Rao et al., 2015; Smith et al., 2011). Presumably, this increased brain activity occurs to compensate for the potentially detrimental influence that APOEe4 may have on cognitive decline (Rao et al., 2015). In addition, the current model of the Scaffolding Theory of Ageing and Cognition posits that lifestyle factors such as physical activity enhance neural scaffolding (Reuter-Lorenz & Park, 2014). Thus, physical activity may help to maintain cognitive function by enhancing neural scaffolding, which may be especially important for APOEe4 carriers who may need to engage greater neural scaffolding in order to overcome the detrimental influence of APOEe4 on cognitive decline.

Present Research

Although some studies suggest that the benefits of physical activity to cognitive decline may be particularly pronounced for APOEe4 carriers, there is no clear consensus. This may be because different studies have assessed different cognitive domains, and many studies have examined only global cognitive functioning. Some cognitive domains appear to be more amenable to the influence of

physical activity and APOEe4 than others. This disparity across different cognitive domains may explain why the interaction between physical activity and APOEe4 has been inconsistent across different studies. In the present study, we aim to overcome this limitation by including several validated cognitive measures to assess a range of cognitive domains.

Additionally, past research has relied predominantly on participants' self-reports as an indication of physical activity levels. Self-report is susceptible to recall bias and response bias, and accurate reporting may be especially challenging amongst older cohorts (Buchman et al., 2012; Prince et al., 2008). Self-reported levels of physical activity are typically higher than objectively measured levels of physical activity (Prince et al., 2008). Additionally, most self-report physical activity questionnaires do not measure non-exercise levels of physical activity, which may be an important contributor to the overall health benefits that amass from physical activity (Levine, 2007; Matthews et al., 2007). Therefore, studies relying on self-report as a measure of physical activity may not accurately capture the true effect of physical activity on cognitive decline.

One study by Buchman et al. (2012) used accelerometers, small devices worn on the body that record movement, to objectively record older adults' levels of physical activity. As predicted, they found that total daily physical activity was inversely associated with rate of cognitive decline, but they did not examine the interaction between physical activity and APOEe4. In the present study, we aim to overcome the limitations associated with self-report measures by using accelerometers to measure total weekly physical activity. Accelerometers are an ideal tool because they can be used to measure physical activity in free-living conditions,

meaning that measurements have high levels of external validity (Aadland & Ylvisåker, 2015), and because they capture total daily levels of physical activity.

The present study was designed to examine the influence of physical activity and APOEe4 on age-related cognitive decline amongst cognitively normal middle aged and older adults. To our knowledge, this is the first study of its kind to employ the use of accelerometers. To further build on past findings and to overcome the limitations of past research, we included several validated cognitive measures to assess a range of cognitive domains, namely long-term memory and learning, working memory, and executive functioning.

On the basis of past research, we predict that participants who are physically active will experience less cognitive domain decline than those who are inactive. We also predict that participants who carry the e4 allele of the APOE gene will experience more cognitive decline than those who do not carry this allele. In line with the Scaffolding Theory of Ageing and Cognition, we predict that any beneficial effect of physical activity on cognitive decline will be more pronounced amongst APOEe4 carriers. This pattern of results has been found previously amongst samples of cognitively normal older adults (Niti et al., 2008; Pizzie et al., 2014; Schuit et al., 2001). This finding would suggest that physical activity helps middle aged and older individuals to maintain cognitive function through compensatory brain processes, and this may be especially so for APOEe4 carriers who may need to engage in greater compensatory processes in order to overcome the potentially detrimental effects of APOEe4 on cognitive decline.

Method

Design

This study utilized a 2 x 2 x 4 mixed design with two between-subjects independent variables, physical activity status (active; inactive) and APOEe4 status (carrier; non-carrier), and one repeated-measures independent variable, phase of assessment (1; 2; 3; 4). The dependent variables were performance on tests of long-term memory and learning, working memory, and executive functioning.

Participants

This study was approved by the Tasmania Health and Medical Human Research Ethics Committee (approval number: H0016623; see Appendix A). Written informed consent was obtained from all participants (see Appendix B). Participants were drawn from a cohort of 513 community-dwelling middle aged and older adults who were participating in the Tasmanian Healthy Brain Project (THBP). The THBP is an ongoing longitudinal study examining the effect of an education intervention in later life on the prevention of age-related cognitive decline and dementia. Participants in the THBP experimental group partake in part-time university study while participants in the control group act as a reference (see Summers et al., 2013). The THBP has been running since 2011, with ongoing participant recruitment. Participants in the THBP have provided genetic samples for testing and have undergone annual cognitive assessments.

The THBP cohort is screened for dementia at each phase of cognitive assessment using the Mattis Dementia Rating Scale (2nd Edition). Those who show cognitive signs of dementia, as indicated by a score less than 132, are excluded from participating (Matteau et al., 2011). Other exclusion criteria comprise conditions that are associated with cognitive impairment, including prior head injury requiring

hospitalisation, multiple sclerosis, epilepsy, cerebrovascular complications such as stroke, aneurysm or transient ischaemic attacks, poorly controlled diabetes, poorly controlled hypertension or hypotension, chronic obstructive pulmonary disease, heart disease, current psychiatric diagnosis, and other neurological disorders such as cerebral palsy or spinal bifida.

Of those who met the THBP inclusion criteria, 53 people volunteered to take part in the current study. However, four participants were excluded from analysis because they did not have APOE genotype data, one participant was excluded because they scored unusually high on a scale of depression, and one participant was excluded because they carried the e2/e4 genotype (and the e2 and e4 alleles appear to have opposing effects on cognition; Small et al., 2004). The final sample consisted of 47 participants (76.6% female; 23.4% male), aged 50-71 at baseline (M = 60.0, SD = 5.8).

Materials

Physical activity measures.

ActiGraph wGT3X-BT accelerometers were used to objectively record levels of total weekly physical activity. These devices continuously record acceleration forces in units of gravity and summarize this acceleration over 60-second epochs. The ActiGraph wGT3X-BT devices are a reliable measure of physical activity amongst adults in free-living conditions (Aadland & Ylvisåker, 2015). Accelerometers were worn during waking hours for seven days, which is an adequate duration to provide reliable measurements of physical activity (Aadland & Ylvisåker, 2015). Accelerometers were worn on an elastic belt around the waist, positioned above the right leg as recommended by Aadland and Ylvisåker (2015).

The accelerometers were accompanied by a written activity diary, which was completed by participants over the seven days of accelerometer wear (see appendix C). The activity diary detailed dates and times of accelerometer wear, times when the accelerometer was removed during the day, any specific activities completed for the purpose of exercise, and the duration of this exercise. The purpose of the activity diary was to record any physical activity that was completed while the accelerometer was not worn.

Demographic measures.

Hospital Anxiety and Depression Scale (HADS): the HADS (Zigmond & Snaith, 1983) was used to assess symptoms of anxiety and depression. The HADS is a self-report questionnaire that asks participants seven questions pertaining to anxiety and seven questions pertaining to depression. Participants respond along a 4-point (0-3) response category, with higher scores indicating greater symptoms of anxiety and depression (Snaith, 2003). Although initially developed for use amongst inpatient populations, the HADS has been demonstrated as a reliable and valid measure of anxiety and depression amongst the general population (Bjelland, Dahl, Haug, & Neckelmann, 2002). Because symptoms of anxiety and depression have been associated with reduced cognitive test performance amongst older adults (Bierman, Comijs, Jonker, & Beekman, 2005), HADS score was recorded at baseline for use as a potential covariate.

Wechsler Test of Adult Reading (WTAR): the WTAR (Wechsler, 2001) was used to estimate pre-cognitive decline full-scale intelligence quotient (FSIQ). The WTAR asks participants to read aloud a list of 50 words that have irregular spelling. A point is afforded for each word correctly pronounced. Scores are co-normed with the Wechsler Adult Intelligence Scale III (WAIS-III; Wechsler, 1997) and a higher

score indicates greater FSIQ. The WTAR is designed to measure aspects of crystallised intelligence, meaning stored knowledge and skills, and thus is thought to be resistant to overall cognitive decline (Green et al., 2008). Because early life IQ is inversely associated with later life cognitive decline (Richards, Shipley, Fuhrer, & Wadsworth, 2004), WTAR estimated FSIQ was recorded at baseline for use as a potential covariate.

Cognitive measures.

A standardised neuropsychological test battery was used to assess long-term memory and learning, working memory, and executive functioning. The tests have been demonstrated as suitable for repeated testing over 12-month retest intervals (Lezak, Howieson, Bigler, & Tranel, 2012; Strauss, Sherman, & Spreen, 2006).

Long-term memory and learning tasks.

Rey Auditory Verbal Learning Test (RAVLT): the RAVLT (Magalhães, Malloy-Diniz, & Hamdan, 2012) is a valid and reliable measure of verbal memory and learning in which participants are presented with a list of 15 words and their recall of these words is tested over five successive trials. The total number of words recalled over the five trials is recorded, with a greater number of words indicating better verbal memory and learning.

Rey Complex Figure Test (three minute recall trial; RCFT): the RCFT (Berry, Allen, & Schmitt, 1991) is a valid and reliable measure of visual memory and learning in which participants examine a complex two-dimensional figure and are asked to reproduce this figure with pen and paper after a three-minute interval. Participants' reproductions of the figure are scored based on the accuracy of the details reproduced, and a higher score indicates better visual learning and memory.

Working memory tasks.

Digit Span (DS): DS is a subtest of the WAIS-III. It assesses short-term memory capacity for auditory-verbal information. Participants are read a sequence of digits and are asked to recall them in the correct order. If recalled correctly, participants are presented with a longer sequence of digits. The greatest number of digits correctly recalled over two trials is recorded, with more digits indicating better working memory.

Letter-Number Sequencing (LNS): LNS is a subtest of the WAIS-III (Wechsler, 1997). It assesses the ability to manipulate auditory-verbal information in short-term memory. Participants are read a sequence of letters and digits (e.g. 5, A, 2 S), and are asked to recall the letters in alphabetical order and the digits in ascending order (e.g. A, S, 2, 5). If recalled correctly, participants are presented with a longer sequence of letters and digits. The longest sequence correctly recalled over two trials is recorded, with a greater number of letters and digits indicating better working memory. As the DSP and LNS subtests of the WAIS-III were used from the outset of the THBP, we have continued to use these tests (rather than the updated WAIS-IV; Wechsler, 2008) for consistency.

Executive functioning tasks.

Controlled Oral Word Association Test (COWAT): the COWAT (Bechtoldt, Benton, & Fogel, 1962) is a valid and reliable measure of verbal fluency, which is involved in executive functioning (Ross et al., 2007). The COWAT captures participants' capacity to spontaneously generate words beginning with a specific letter. It consists of three letter trials, F, A, and S, and participants have 60 seconds on each trial to generate as many words beginning with the particular letter as possible. The total number of words generated over the three trials is recorded, with a

greater number of words indicating better executive functioning (Ruff, Light, Parker, & Levin, 1996).

Stroop Colour-Word Test (24-item Victoria version; VST): the VST (Stroop, 1935) is a psychometrically strong measure of executive function (Troyer, Leach, & Strauss, 2009), which assesses the speed of processing and inhibitory control for visual information. The test consists of three trials. On the first trial, participants are presented with a sequence of coloured dots and are asked to name the colour of each dot as quickly as possible. On the second trial, participants are presented with a sequence of random words printed in coloured ink and are asked to name the colours of the ink as quickly as possible. On the third trial, participants are presented with a sequence of colour words printed in coloured ink. The colour words do not correspond to the colours of the ink. Participants are asked to name the colours of the ink (ignoring the colour words printed) as quickly as possible. The time difference (in seconds) between trial three and trial one indicates Stroop interference, and thus lower scores indicate better executive functioning.

Trail Making Test (part B; TMT): the TMTB (Reitan & Wolfson, 1985) is a valid and reliable measure of executive functioning (Sanchez-Cubillo et al., 2009), assessing divided attention on a visuo-motor task. Participants are presented with a piece of paper that has printed letters and numbers scattered over the page. Participants are asked to draw lines to connect the letters and numbers together in ascending order (e.g. 1-A-2-B-3-C-4-D and so on) as quickly as possible. Performance on the TMTB is measured in seconds, and thus lower scores indicate better executive functioning.

Procedure

To recruit participants, an invitation to participate was placed in the THBP newsletter, which was emailed or mailed to each participant depending on participant preference. Individual invitations to participate were also emailed or mailed to participants (see Appendix D).

To measure total weekly levels of physical activity, participants were sent an accelerometer, written instructions, seven-day activity diary, and reply-paid postage bag. Participants were asked to wear the accelerometer during waking hours for seven consecutive days. As the accelerometers are not waterproof, participants removed devices for water activities such as swimming and showering. After seven days, participants returned the accelerometer along with the signed consent form and activity diary via post.

Using Access computer software, we applied the Freedson equation to translate raw acceleration data into weekly minutes spent in light, moderate, and vigorous physical activity, based on metabolic equivalent minute (MET) values (Freedson, Melanson, & Sirard, 1998). Any physical activity that was completed while the accelerometer was not worn was compared to the 2011 Compendium of Physical Activities (Ainsworth et al., 2011) to estimate MET values. Total weekly minutes spent in moderate and vigorous physical activity were then compared to the World Health Organization's Global Recommendations on Physical Activity for Health (2010). Participants who met or exceeded the recommended weekly target of 150 minutes of moderate physical activity or 75 minutes of vigorous physical activity (or an equivalent combination of the two) were grouped as active. Participants who did not reach this target were grouped as inactive.

Participants were also asked to complete the Incidental and Planned Exercise Questionnaire (weekly average version; IPEQ-WA; Delbaere, Hauer, & Lord, 2010), and the Historical Leisure Activities Questionnaire (HLAQ; Kriska et al., 1988). The IPEQ-WA is a self-report questionnaire that asks participants to indicate their typical weekly physical activity for the past three months. The HLAQ is a self-report questionnaire that asks participants to indicate the frequency and duration with which they engaged in a range of activities over their lifetime. The questionnaires were completed via Survey Monkey or via mail-out, depending on participant preference. Responses to these questionnaires are beyond the scope of this study and therefore will not be discussed.

Participants provided salivary samples to the THBP team for DNA extraction. To determine APOE genotype, PCR analysis was conducted as described by Donohoe, Salomäki, Lehtimäki, Pulkki, and Kairisto (1999). Participants were grouped as APOEe4 carriers (e3/e4; e4/e4 genotypes) and non-APOEe4 carriers (e2/e2; e2/e3; e3/e3 genotypes). There is evidence to suggest that the e2 allele of the APOE gene is protective against age-related cognitive decline (Small et al., 2004). Therefore, to eliminate the potentially confounding influence of APOEe2 on cognitive decline, we excluded participants with the e2/e4 genotype from analysis.

Administration of the neuropsychological test battery occurred annually through the THBP. Assessments that took place at baseline and over the proceeding three years were used to examine cognitive test performance across each assessment phase. Participants consented to have their genetic data and cognitive data released to us as part of the informed consent process, and data was de-identified by the THBP project manager prior to its release.

Data Screening and Analysis

All analyses were conducted using SPSS version 21. Initially, 53 participants took part in the study. However, four participants were excluded because they did not have APOE genotype data, and one participant was excluded because they carried the e2/e4 genotype.

Continuous demographic variables (age; body mass index; years of education; HADS anxiety; HADS depression; WTAR estimated FSIQ) were tested at baseline for skew and outliers. There was one extreme outlier on the HADS depression sub-scale that was more than four standard deviations above the mean. Because depression has a global negative effect on cognitive test performance (Bierman, Comijs, Jonker, & Beekman, 2005), we excluded this participant from analysis. After excluding data from this participant, all demographic variables were normally distributed. Thus, a total of 47 participants were included in the final analyses.

Continuous dependent variables (RAVLT score; RCFT score; DS score; LNS score; COWAT score; VST interference; and TMTB time) were tested at each assessment phase for outliers and skew. On at least one assessment phase, there were outliers on RAVLT score, RCFT score, LNS score, VST interference, and TMTB time. On at least one assessment phase, RAVLT scores and RCFT score were negatively skewed, and VST interference and TMTB time were positively skewed. Square-root transformations were performed to control for skew. However, as these transformations did not alter the results and maximum likelihood estimation is robust to non-normality (Enders, 2001), final analyses were conducted using the untransformed data.

We compared APOE genotype proportions of the sample to estimated genotype proportions of the worldwide population (Zannis et al., 1993), and the sample distribution did not significantly differ from a Hardy-Weinberg equilibrium, $\chi^2(5) = 8.60$, $p = .126$, $V = .43$ (Table 1). Differences in demographic characteristics between the four physical activity/e4 groups were also checked using chi-square tests of independence for categorical variables and one-way analyses of variance (ANOVAs) for continuous variables. There were no significant differences between groups (Table 2).

Table 1

Frequency of APOE Genotypes Found in the Worldwide Population and in the Current Sample

Frequency	e2/e2	e2/e3	e2/e4	e3/e3	e3/e4	e4/e4
Estimated worldwide (%)	1.2	15.8	3.7	51.8	24.5	2.9
Sample (%)	0.0	6.4	0.0	59.6	34.0	0.0

As some participants had missing cognitive data on one or more assessment phase, we used full information maximum likelihood ANOVAs to accommodate for missing values (Enders, 2010). We conducted a series of three-way mixed ANOVAS to test for interaction effects between physical activity status (active; inactive), APOEe4 status (carrier; non-carrier), and assessment phase (1; 2; 3; 4) on performance on each of the cognitive tests.

Table 2

Demographic Characteristics of Active and Inactive Groups by APOEe4 Carrier Status

Characteristic	Active		Inactive		χ^2/F (df)	*p*
	e4 carriers (*N* = 13)	Non-e4 carriers (*N* = 27)	e4 carriers (*N* = 3)	Non-e4 carriers (*N* = 4)		
Sex, *n* (%)						
Female	10 (76.9)	20 (74.1)	3 (100.0)	3 (75.0)	$\chi^2(3) = 1.02$	.797
Male	3 (23.1)	7 (25.9)	0 (0.0)	1 (25.0)		
THBP group, *n* (%)						
Experimental	9 (69.2)	23 (85.2)	1 (33.3)	3 (75.0)	$\chi^2(3) = 4.64$	.200
Control	4 (30.8)	4 (14.8)	2 (66.7)	1 (25.0)		
Age, *M (SD)*	60.9 (5.1)	58.5 (5.6)	63.0 (9.5)	64.0 (5.4)	$F(3, 43) = 1.61$	.202
BMI, *M (SD)**	25.2 (3.8)	25.5 (4.6)	19.0 (0.3)	29.0 (1.6)	$F(3, 38) = 2.31$	.092
Years of education, *M (SD)*	14.0 (3.0)	14.4 (2.4)	12.7 (1.5)	15.8 (3.8)	$F(3, 43) = 0.83$	.483
HADS depression, *M (SD)*	2.4 (1.6)	1.7 (1.5)	3.0 (2.0)	1.3 (1.0)	$F(3, 43) = 1.38$	.263
HADS anxiety, *M (SD)*	5.2 (2.3)	5.2 (2.7)	5.0 (2.6)	4.3 (2.2)	$F(3, 43) = 0.18$	.912
WTAR estimated FSIQ, *M (SD)*	111.0 (6.4)	112.9 (3.9)	110.3 (7.1)	114.3 (4.5)	$F(3, 43) = 0.79$	.506

Note. THBP = Tasmanian Healthy Brain Project; BMI = body mass index; HADS = Hospital Anxiety and Depression Scale; WTAR = Wechsler Test of Adult Reading; FSIQ = full-scale intelligence quotient.

**N*(active e4 carriers) = 11; *N*(active non-e4 carriers) = 26; *N*(inactive e4 carriers) = 2; *N*(inactive non-e4 carriers) = 3. Five participants did not have BMI data.

Results

All effects and differences are reported as significant at $p < .05$ unless otherwise stated.

Long-term Memory and Learning

For both measures of long-term memory and learning, there were no significant main effects of physical activity status or APOEe4 status, indicating that overall RAVLT score and RCFT score was similar between each of the physical activity groups and each of the APOEe4 groups. There was a significant main effect of assessment phase on RAVLT score. Pairwise comparisons revealed that RAVLT score increased from phase 2 to phase 3 ($p = .013$, $g = 0.34$), and this was a small effect. However, this difference was not significant after considering a Bonferroni-adjusted p-value of .008 to control for Type I error. There was also a significant main effect of assessment phase on RCFT score. Pairwise comparisons revealed that RCFT score significantly increased from phase 1 to phase 2 ($p < .001$, $g = 0.60$), and again from phase 2 to phase 3 ($p = < .001$, $g = 0.54$), using a Bonferroni-adjusted p-value of .008, and these were medium effects. These improved performances over phases of assessment indicate possible practice and learning effects. Mean RAVLT scores and RCFT scores at each assessment phase are shown in Table 3.

Table 3

Mean Scores on the Rey Auditory Verbal Learning Test and Rey Complex Figure Test at Each Assessment Phase

		RAVLT		RCFT	
Phase	*N*	*M*	95% CI	*M*	95% CI
1	47	52.4	[49.2, 55.6]	22.3	[20.2, 24.4]
2	44	50.0	[46.8, 53.2]	26.7	[24.5, 28.8]
3	45	53.8	[50.4, 57.2]	30.6	[28.3, 32.8]
4	45	53.6	[50.3, 56.9]	31.1	[28.9, 33.3]

Note. RAVLT = Rey Auditory Verbal Learning Test; RCFT = Rey Complex Figure Test; CI = confidence interval.

For both measures of long-term memory and learning, there were no significant two-way interactions between physical activity status and assessment phase, or APOEe4 status and assessment phase, indicating that the effects of assessment phase on RAVLT score and on RCFT score were not influenced by whether participants were active or inactive, or whether or not they carried the APOEe4 allele. There were also no significant two-way interactions between physical activity status and APOEe4 status. Finally, there were no significant three-way interactions between physical activity status, APOEe4 status, and assessment phase. All estimated fixed effects for the ANOVA results are shown in Table 4.

Table 4

Fixed Effects Estimates for Analysis of Variance Results for Measures of Long-term Memory and Learning

Variable	*F* (df within, error)	*p*
RAVLT		
Physical activity status	2.82 (1, 47.84)	.100
ApoEe4 status	0.07 (1, 47.84)	.791
Assessment phase	**2.89 (3, 135.14)**	**.039**
Physical activity * phase	0.67, (3, 135.14)	.574
ApoEe4 * phase	1.17 (3, 135.14)	.323
Physical activity * ApoEe4	0.14 (1, 47.84)	.713
Physical activity * ApoEe4 * phase	2.46 (3, 135.14)	.065
RCFT		
Physical activity status	0.65 (1, 47.28)	.423
ApoEe4 status	1.20 (1, 47.28)	.280
Assessment phase	**30.92 (3, 134.69)**	**<.001**
Physical activity * phase	0.80 (3, 134.69)	.494
ApoEe4 * phase	1.13 (3, 134.69)	.338
Physical activity * ApoEe4	2.26 (1, 47.28)	.139
Physical activity * ApoEe4 * phase	0.28 (3, 134.69)	.840

Note. Significant effects at the $p < .05$ level are in boldface. RAVLT = Rey Auditory Verbal Learning Test; RCFT = Rey Complex Figure Test.

Working Memory

For both measures of working memory, there were no significant main effects of physical activity status or APOEe4 status, indicating that overall DS score and LNS score was similar between each of the physical activity groups and each of the APOEe4 groups. There was a significant main effect of assessment phase on DS score. But, there was no significant main effect of assessment phase on LNS score, indicating that LNS score was similar at each phase of assessment.

There was a significant two-way interaction effect between physical activity status and assessment phase on DS score. Pairwise comparisons revealed that for active participants, DS score was greater at phase 4 than at phase 3 (p = .020, g = 0.28), at phase 2 (p = .021, g = 0.29), and at phase 1 (p = .007, g = 0.33), and these were small effects. However, these comparisons were not significant after considering a Bonferroni-adjusted p-value of .004. For inactive participants, DS score decreased from phase 1 to phase 2 (p = .002, g = 0.90), which was a large effect, and increased from phase 2 to phase 4 (p = .022, g = 0.70), which was a medium effect. However, only the phase 1 vs. phase 2 comparison was significant after using a Bonferroni-adjusted p-value of .004. Mean DS scores at each assessment phase for active and inactive participants are shown in Figure 1.

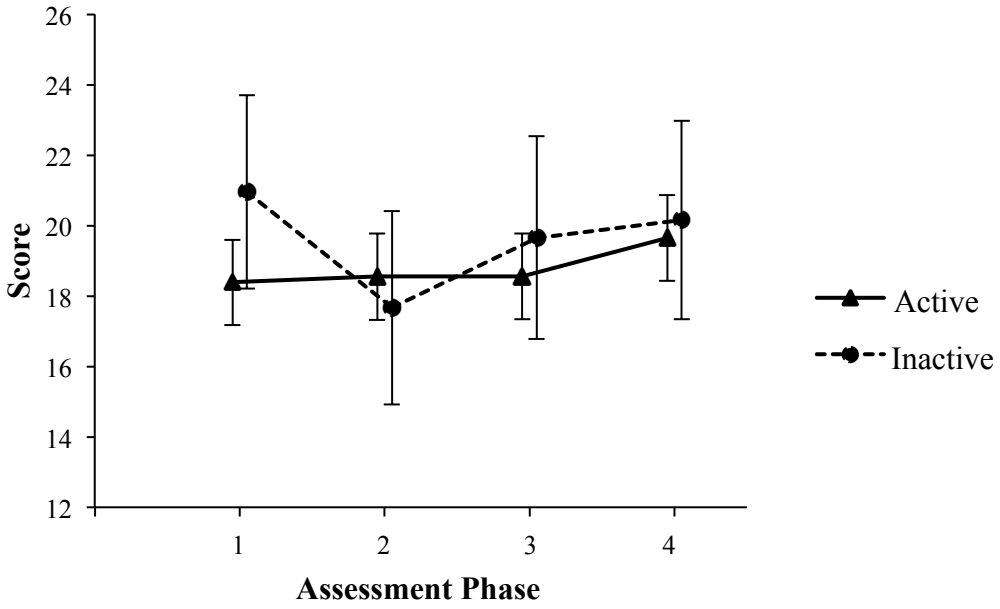

Figure 1. Mean Digit Span score at each assessment phase for active and inactive participants. Error bars represent 95% confidence intervals. Points are offset horizontally so that error bars are visible.

There was no significant two-way interaction effect between physical activity status and assessment phase on LNS score. For both measures of working memory, there were no significant two-way interactions between APOEe4 status and assessment phase, or between physical activity status and APOEe4 status. Finally, there were no significant three-way interactions between physical activity status, APOEe4 status, and assessment phase, indicating that the interaction between physical activity and assessment phase on DS score did not significantly differ between APOEe4 carriers and non-APOEe4 carriers. All estimated fixed effects for the ANOVA results are shown in Table 5.

Table 5

Fixed Effects Estimates for Analysis of Variance Results for Measures of Working Memory

Variable	*F* (df within, error)	*p*
DS		
Physical activity status	0.38 (1, 47.37)	.543
ApoEe4 status	0.31 (1, 47.37)	.580
Assessment phase	**3.83 (3, 134.57)**	**.011**
Physical activity * phase	**3.17 (3, 134.57)**	**.026**
ApoEe4 * phase	0.30 (3, 134.57)	.825
Physical activity * ApoEe4	0.15 (1, 47.37)	.701
Physical activity * ApoEe4 * phase	0.60 (3, 134.57)	.616
LNS		
Physical activity status	0.34 (1, 47.57)	.565
ApoEe4 status	1.27 (1, 47.57)	.266
Assessment phase	0.27 (3, 134.82)	.844
Physical activity * phase	0.17 (3, 134.82)	.916
ApoEe4 * phase	0.76 (3, 134.82)	.520
Physical activity * ApoEe4	0.03 (1, 47.57)	.874
Physical activity * ApoEe4 * phase	0.27 (3, 134.82)	.846

Note. Significant effects at the $p < .05$ level are in boldface. DS = Digit Span; LNS = Letter-Number Sequencing.

Executive Functioning

For all measures of executive functioning, there were no significant main effects of physical activity status or APOEe4 status, indicating that overall COWAT score, VST interference, and TMTB time were similar between each of the physical activity groups and each of the APOEe4 groups. There was a significant main effect of assessment phase on VST interference. But, there were no significant main effects of assessment phase on COWAT score or TMTB time, indicating that COWAT score and TMTB time was similar at each phase of assessment.

There was a significant two-way interaction effect between physical activity status and assessment phase on VST interference. Pairwise comparisons revealed that for active participants, VST interference significantly decreased between phase 1 and phase 4 (p = .003, g = 0.45), using a Bonferroni-adjusted p-value of .004, and this was a small to medium effect. For inactive participants, VST interference was significantly greater at phase 3 than at phase 1 (p = .016, g = 1.02), at phase 2 (p = .005, g = 1.21), and at phase 4 (p = .010, g = 1.15). Although these were large effects, these comparisons were not significant after using a Bonferroni-adjusted p-value of .004. Mean VST interference at each assessment phase for active and inactive participants are shown in Figure 2.

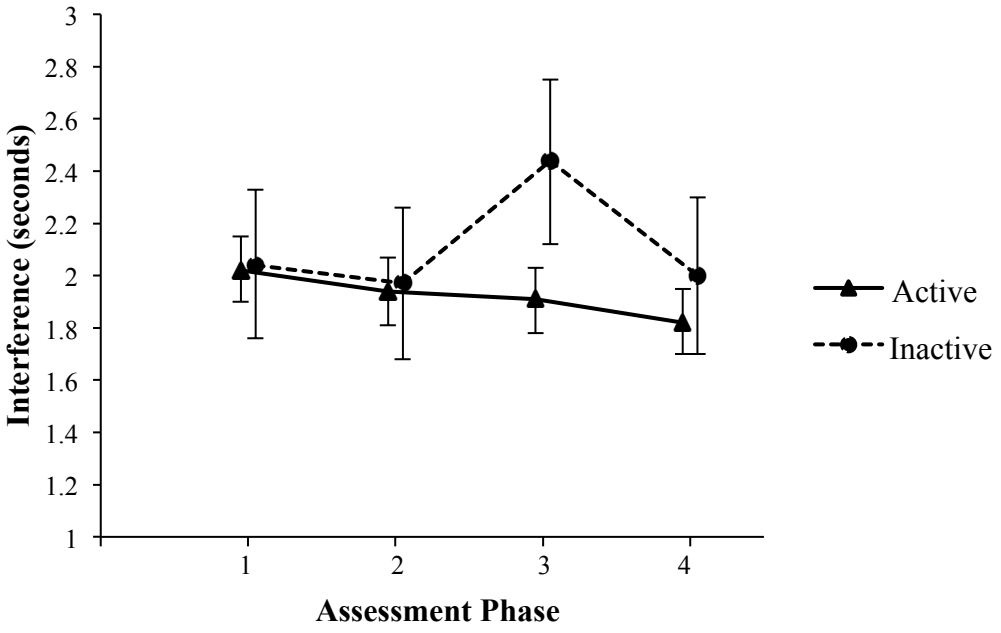

Figure 2. Mean VST interference at each assessment phase for active and inactive participants. Error bars represent 95% confidence intervals. Points are offset horizontally so that error bars are visible.

There was no significant two-way interaction effect between physical activity status and assessment phase on COWAT score or TMTB time. For all three measures of executive functioning, there were no significant two-way interactions between APOEe4 status and assessment phase, or between physical activity status and APOEe4 status

Finally, there were no significant three-way interactions between physical activity status, APOEe4 status, and assessment phase, indicating that the interaction effect between physical activity and assessment phase on VST interference did not significantly differ between APOEe4 carriers and non-APOEe4 carriers. All estimated fixed effects for the ANOVA results are shown in Table 6.

Table 6

Fixed Effects Estimates for Analysis of Variance Results for Measures of Executive Functioning

Variable	*F* (df within, error)	*p*
COWAT		
Physical activity status	0.57 (1, 47.80)	.454
ApoEe4 status	0.30 (1, 47.80)	.587
Assessment phase	2.05 (3, 135)	.110
Physical activity * phase	0.92 (3, 135)	.433
ApoEe4 * phase	0.83 (3, 135)	.481
Physical activity * ApoEe4	.001 (1, 47.80)	.976
Physical activity * ApoEe4 * phase	1.08 (3, 135)	.361
VST		
Physical activity status	2.27 (1, 47.38)	.139
ApoEe4 status	3.77 (1, 47.38)	.058
Assessment phase	**3.21 (3, 134.93)**	**.025**
Physical activity * phase	**3.61 (3, 134.93)**	**.015**
ApoEe4 * phase	0.51 (3, 134.93)	.674
Physical activity * ApoEe4	3.67 (1, 47.38)	.061
Physical activity * ApoEe4 * phase	0.30 (3, 134.93)	.827
TMTB		
Physical activity status	0.04 (1, 47.33)	.844
ApoEe4 status	0.01 (1, 47.33)	.923
Assessment phase	1.70 (3, 134.55)	.171
Physical activity * phase	0.80 (3, 134.55)	.496
ApoEe4 * phase	0.41 (3, 134.55)	.746
Physical activity * ApoEe4	0.03 (1, 47.33)	.872
Physical activity * ApoEe4 * phase	0.56 (3, 134.55)	.641

Note. Significant effects at the $p < .05$ level are in boldface. COWAT = Controlled Oral Word Association Test; VST = Victoria Stroop Test; TMTB = Trail Making Test (part B).

Discussion

The present study was designed to examine the influence of objectively measured physical activity and APOEe4 on age-related cognitive decline amongst cognitively normal middle aged and older adults. We predicted that participants who were physically active would experience less cognitive decline than those who were inactive, and that participants who carried APOEe4 would experience more cognitive decline than those who did not carry this allele. On the basis of past research (Niti et al., 2008; Pizzie et al., 2014; Schuit et al., 2001) and the Scaffolding Theory of Ageing and Cognition, we also predicted that any beneficial effect of physical activity on cognitive decline would be more pronounced amongst APOEe4 carriers than non-APOEe4 carriers.

Present Findings

Results of the present study revealed significant interaction effects between physical activity and assessment phase on DS and VST performance. Results revealed that inactive participants showed some significant short-term performance decline on DS, and active participants showed some significant performance improvement on the VST. Generally, active participants' performance on the DS and VST remained steady or improved across each phase of assessment, while inactive participants' performance tended to fluctuate. This general pattern of results is consistent with our hypothesis that active participants would experience less cognitive decline than inactive participants. However, these changes in cognitive performance were not consistent across every phase of assessment, and the interaction was not present for every test of working memory and of executive functioning, which is what we would expect if there were a true consistent effect of physical activity on these domains of cognition. Thus, results suggest that physical

activity does not have a consistent long-term effect on normal age-related cognitive decline.

This finding is inconsistent with previous research, which shows a consistent protective effect for all levels of physical activity on overall cognitive decline (e.g. Best et al., 2017; Sofi et al., 2010). Previous research also shows that physical activity seems to be particularly beneficial to executive functioning and processing speed amongst groups of cognitively normal individuals (Netz et al., 2011; Wilbur et al., 2012). This finding was not replicated in the present study, with results showing no consistent effect of physical activity across the three tests of executive functioning. Few reported studies show no significant effect of physical activity on neurocognitive health (Gidicsin et al., 2015). However, this may be a result of publication bias, meaning that statistically significant results are more likely to be published than non-significant results (Dick et al., 2015).

Across all cognitive domains, there were no significant interaction effects between APOEe4 status and assessment phase. This finding is inconsistent with our hypothesis that APOEe4 carriers would experience more cognitive decline than non-APOEe4 carriers. This suggests that APOEe4 does not influence age-related cognitive decline amongst healthy middle-aged and older adults.

Previous research shows inconsistent findings. Some studies suggest that the presence of APOEe4 has a detrimental effect on cognitive decline in normal ageing (Caselli et al., 2004; Caselli et al., 2007; Wisdom, Callahan, & Hawkins, 2011). However, this influence has been relatively small and specific to the domains of episodic memory and executive functioning (Small et al., 2004). Other studies have reported no independent effect of APOEe4 on cognition amongst healthy older adults

(Foster et al., 2013; Ward et al., 2014; Quintas et al., 2014), consistent with findings of the present study.

Across all cognitive domains, there were no significant interactions between physical activity status, e4-carrier status, and phase of cognitive assessment. This finding is inconsistent with our hypothesis that any beneficial effect of physical activity on cognitive decline would be more pronounced amongst APOEe4 carriers than non-APOEe4 carriers. This suggests that the combination of physical activity and presence or absence of APOEe4 does not influence age-related cognitive decline amongst healthy middle-aged and older adults.

Past research has typically found significant interactions between physical activity and APOEe4. However, the nature of these interactions has been inconsistent and effect sizes have often been small (Wisdom et al., 2011). Some studies show that physical activity is associated with reduced decline in cognitive functioning, and that this is effect is more pronounced for APOEe4 carriers (Niti et al., 2008; Pizzie et al., 2014; Schuit et al., 2001; Thibeau et al., 2017; Woodward et al., 2012). However, other studies show that the benefits of physical activity to later-life cognition are more pronounced for non-APOEe4 carriers (Obisesan et al., 2012; Podewils et al., 2005). Both of these patterns of results are inconsistent with the findings of the present study. Few reported studies show no significant interaction effect between physical activity and APOEe4 on cognitive decline.

Possible Explanations

Previous research has largely focused on the influence of physical activity and APOEe4 on pathological cognitive decline. A meta-analysis by Guure, Ibrahim, Adam, and Said (2017) found that the protective effects of physical activity are much larger for dementia and Alzheimer's disease than for non-pathological cognitive

decline. Additionally, APOEe4 has been demonstrated a major risk factor for Alzheimer's disease (Farrer et al., 1997), but the effect of APOEe4 on normal age-related cognitive decline has been inconsistent and effect sizes have often been small (Small et al., 2004). These inconsistent results may be because previous studies may have included pre-clinical dementia cases in their samples (Small et al., 2004). It is possible that findings of the present study showed no consistent effects of physical activity and APOEe4 on normal age-related cognitive decline because these factors only influence pathological cognitive decline, and are not important to non-clinical decline.

Another possible explanation of the present findings is that there may be a dose-response relationship between APOEe4 and cognitive decline. There is some evidence to suggest that APOEe4 has a dose-response relationship with cognitive decline in Alzheimer's disease, with APOEe4 homozygotes experiencing a greater rate of disease-related decline than APOEe4 heterozygotes (Martins et al., 2005). It is possible that this dose-response relationship is also present in normal ageing. Indeed, Etnier et al. (2007) found that aerobic fitness was significantly associated with memory performance amongst APOEe4 homozygotes, but not amongst APOEe4 heterozygotes, in a healthy sample of older women. Due to the relatively low population frequency of APOEe4 (17%; Zannis et al., 1993), we were only able to dichotomise participants into APOEe4 carriers and non-APOEe4 carriers, and indeed did not have any APOEe4 homozygotes in our sample. Therefore, we were unable to directly examine the possibility of an APOEe4 allele dose-response relationship. It is possible that there is an interaction between physical activity and the APOEe4 allele (consistent with previous research), but that this interaction is only apparent for those at greatest genetic risk of increased cognitive decline. Additionally, all participants

were aged 50-71 years and our sample did not include any individuals in the older stages of late adulthood. A meta-analysis by Wisdom et al. (2017) found that the detrimental effects of the e4 allele increase with age. It is possible that we did not find any significant effects of the e4 allele amongst our sample because any potential effects of the e4 allele may not become apparent until older age.

Another possible explanation of our findings is that the demographic characteristics of our sample may have been sufficiently protective of cognitive decline, so that physical activity and APOEe4 had no additional effect. For example, Rovio et al. (2005) found that physical activity at midlife was associated with a reduced risk of dementia and Alzheimer's disease in later life, especially for APOEe4 carriers. However, this interaction between physical activity andAPOEe4 was not significant after researchers controlled for a range of other factors such as education and medical history.

In the present study, participants were excluded if they had a history of medical issues associated with cognitive impairment, and our final sample consisted of participants who had, on average, a high level of education, and above average estimated FSIQ (see Table 2). It is also possible that there was a participation bias, meaning that participants who volunteered to take part in the study may have had higher levels of motivation and may have been more engaged with their community. Education, FSIQ, and social engagement have each been positively associated with greater cognitive function in later life (Karama et al., 2014; Krueger et al., 2009; Lee, Kawachi, Berkman, & Grodstein, 2003). According to the Scaffolding Theory of Ageing and Cognition, lifestyle factors such as learning and social engagement enhance neural scaffolding, which in turn helps to maintain cognitive function in later life (Reuter-Lorenz & Park, 2014). Thus, it is possible that the cognitive health

of our sample was sufficiently high that any additional effects of physical activity and the e4 allele on cognition were not evident.

Furthermore, high levels of physical activity tend to coincide with other protective factors. For example, physical activity is associated with higher levels of education, younger age, absence of chronic health conditions, and lower levels of psychological distress amongst older adults (Kaplan, Newsom, McFarland, & Lu, 2001). Thus, it is possible that the independent association of physical activity with later-life cognition is weaker than previously reported. The previously reported effects of physical activity on cognition may have been a result of these potentially confounding factors rather than any physiological influence of physical activity itself. In the present study, it is possible that we did not find any consistent effects of physical activity on cognitive decline because all participants were similar in age, level of education, estimated FSIQ, and levels of reported anxiety and depression.

In terms of the significant interaction effects between physical activity and assessment phase on DS and VST performance, one possible explanation of these findings is the small size of our inactive group. Of 47 participants, only 7 were grouped as inactive. This means that the cognitive scores of one or two inactive participants may have exerted a strong influence on the overall mean of the group, and may explain why the inactive group showed an inconsistent pattern of cognitive performance on DS and VST.

Alternatively, another potential explanation is that physical activity may indirectly benefit cognitive test performance through its positive influence on the ability to allocate and monitor attention resources (Hillman, Belopolsky, Snook, Kramer, & McAuley, 2004). Inactive individuals may experience difficulty paying sustained attention to cognitive tasks, leading them to show an inconsistent pattern of

performance across each phase of assessment and across each cognitive test. Although we would expect fluctuations in attention to be averaged across participants, this may not have occurred due to the small size of our inactive group. Furthermore, as attention decreases with age (Sofi et al., 2010), it is possible that the inconsistent pattern of performance on DS and VST demonstrated by the inactive group is reflective of age-related decline in attentional processes.

Limitations

Findings should be interpreted in light of the study's limitations. Firstly, to measure cognitive decline, we used data from cognitive assessments that had previously taken place. However, we categorized participants as active or inactive based on their present level of physical activity. It is possible that participants' current levels of physical activity were not representative of their prior levels of activity. Some participants in the active group may have been inactive at the time of cognitive assessment, although it is more likely that some participants who were classed as inactive may have been active at the time of cognitive assessment, as physical activity typically decreases with age (Kaplan et al., 2001). If this were the case, any possible differences in cognitive decline between the active and inactive groups would be minimized in the current sample. This may explain why results did not show any consistent long-term effects of physical activity.

It is also noteworthy that over 80% of participants in the present sample were grouped as physically active. However, less than 45% of the general Australian population aged over 50 years engages in the recommended level of physical activity (Australian Bureau of Statistics, 2013). Therefore, the high number of physically active participants in our sample is atypical. We used accelerometers to objectively record physical activity, thus eliminating the potential for recall bias that is

associated with self-report measures. However, it is possible that participants may have increased their physical activity levels throughout the duration of the study because they were aware that their activity levels were being recorded. Additionally, some participants may have recently increased or decreased their physical activity in response to subjective changes in their cognitive function. Future research could overcome this limitation by including a measure of physical activity at each phase of cognitive assessment, or by including a physical activity intervention for more accurate groupings of active and inactive participants.

Related to the aforementioned point, this study is further limited by its small sample size and uneven group sizes, which may have compromised the robustness of ANOVAs (Dick et al., 2015; Field, 2018). Furthermore, due to the small sample size, our study may not have had adequate power to detect a true interaction between physical activity and APOEe4. This is a common problem in genetic research as population frequencies of the allele in question are often low (Dick et al., 2015). Additionally, participants showed little variation in demographic variables, and were screened for any medical conditions associated with cognitive impairment. This may have been compounded further by participation bias, as our participants were not randomly selected from the wider population. As a result, our sample may not be representative of the general population.

A possible limitation of this study is that we included physical activity as a categorical variable. Those who engaged in the recommended amount of moderate and vigorous activity were classed as active, thereby aligning with the World Health Organization's physical activity guidelines. However, it is possible that any benefits of physical activity to cognition are only evident at high levels of activity. Middleton et al. (2011) found a dose-response relationship between total daily energy

expenditure from activity and incidence of cognitive impairment, such that greater energy expenditure was associated with a reduced incidence of cognitive impairment. It is possible that there is a similar dose-response relationship between physical activity and normal age-related cognitive decline that could not be detected in our dichotomized sample. Future research could overcome this limitation by measuring physical activity along a continuous scale, or by grouping participants into low, moderate, and high physical activity groups for a more nuanced exploration of the effect of physical activity.

Contributions

This study has made some notable contributions to the research field of age-related cognitive decline. To our knowledge, this is the first study of physical activity, APOEe4, and cognitive decline to employ the use of accelerometers. Past studies have relied on self-report questionnaires (e.g. Niti et al., 2008; Obisesan et al., 2012; Schuit et al., 2001), or have measured participants' physical fitness to indirectly estimate level of physical activity (e.g. Etnier et al., 2007). Accelerometers offer benefits over both of these methods because they provide a direct objective measure of physical activity, and can be used to record participants' behaviour in free-living conditions. Accelerometers also capture total daily physical activity, not only physical activity from exercise. This is important because non-exercise physical activity is an important contributor to physical health (Levine, 2007; Matthews et al., 2007), and therefore it is probable that it is beneficial to neurocognitive health as well.

When using accelerometers to examine the influence of physical activity on cognition it is important to be mindful that the accelerometers also capture work-related physical activity. Manual labour-based work has been associated with a lower

level of educational attainment (Rovio et al., 2007). Thus, studies using accelerometers to examine the influence of physical activity on cognition should be mindful of the potentially confounding influence of education. However, in the present study the active and inactive groups reported a similar level of education. Thus, the use of accelerometers to objectively measure physical activity is a particular strength of this study.

Furthermore, the majority of past research into later-life cognition has focused on the pathological cognitive decline present in dementia and Alzheimer's disease. However, identifying factors that may be associated with age-related cognitive decline, prior to clinically significant cognitive impairment, may be more effective at reducing the burden of dementia and Alzheimer's disease than current approaches. Additionally, normal age-related cognitive decline can be distressing for individuals to experience. An understanding of the modifiable factors that may be associated with cognitive decline could be of benefit to older adults who wish to delay or slow normal age-related cognitive decline. Thus, this study has contributed to the field of cognition research by examining normal, non-pathological cognitive decline.

Finally, previous studies have either relied on the MMSE to assess global cognitive decline (e.g. Obisesan et al., 2012; Podewils et al., 2005), or have examined only one aspect of cognition (e.g. Thibeau et al., 2017; Etnier et al., 2007). However, some cognitive domains may be more influenced by physical activity and APOEe4 than others. Furthermore, many previous longitudinal studies have only included one follow-up cognitive assessment and follow-up periods have often been short, ranging from one to three years (Niti et al., 2008; Schuit et al., 2001; Woodward et al., 2012). To overcome these limitations, we chose to assess

performance on a range of cognitive tests annually over four years to provide a comprehensive and in-depth assessment of cognitive decline. Thus, the longitudinal and domain-specific measurement of cognitive decline is a particular strength of this study.

Future Directions

Future research would benefit from investigating the influence of lifetime physical activity on age-related cognitive decline, and potential interactions with APOEe4. The present study examined only middle-aged and older adults' current levels of physical activity, and few studies have examined the influence of lifetime physical activity on late-life cognition and its interaction with APOEe4. As normal age-related cognitive decline begins prior to the age of 60 (Salthouse, 2009) and memory decline can become accelerated for APOEe4 carriers from as early as 50 years (Caselli et al., 2004), it is probable that early life physical activity is an important determinant of later-life cognitive function.

Indeed, Chang et al. (2010) found that being physically active during mid-life is associated with better executive functioning, a faster speed of processing, and better memory in later-life, compared to being inactive. Additionally, Middleton, Barnes, Lui, and Yaffe (2010) found that women who reported being physically active at any point over their lifetime had a lower likelihood of cognitive impairment in late-life, compared to those who were inactive. Interestingly, teenage physical activity was most strongly associated with reduced odds of late-life cognitive impairment than physical activity during any other age. Examining whether lifetime physical activity interacts with APOEe4 to influence age-related cognitive decline would be beneficial.

Future research would also benefit from examining whether different types of physical activity have differential effects on cognition. In the present study, we measured only total daily physical activity, and few studies have examined the influence of different types of activity on cognition. One study conducted by Bossers et al. (2015) showed that aerobic training coupled with strength training was more effective than aerobic-only training at reducing cognitive decline in those with dementia. It is possible that strength training in particular may be beneficial in reducing normal age-related cognitive decline. Furthermore, it is possible that some of the previously reported benefits of physical activity were attributable to the social engagement and cognitive stimulation that is often coupled with physical activity, rather than the physiological influence of physical activity itself. Future research could investigate this possibility by employing a physical activity intervention, where groups of participants attend weekly aerobic, strength, and flexibility classes, and a control group attends weekly social gatherings.

Conclusion

The present study was designed to examine the influence of physical activity and APOEe4 on age-related cognitive decline amongst a sample of middle-aged and older adults. Understanding the factors that may influence age-related cognitive decline may be beneficial in identifying areas to implement potential prevention interventions.

Past research in this area has been limited by its use of self-report questionnaires to measure physical activity, by its focus on pathological cognitive decline, and by its use of the MMSE to assess cognitive function. The present study overcame these limitations by using accelerometers to objectively record participants' levels of total weekly physical activity, by assessing cognitive decline

amongst a cognitively normal sample, and by using a range of validated tests to assess the cognitive domains of long-term memory and learning, working memory, and executive functioning. However, this study was limited by the delay between administering cognitive assessments and physical activity assessments, by the relatively small sample size and uneven group sizes, and possibly by its categorical measure of physical activity.

In closing, findings indicated that physical activity, APOEe4, or combinations of the two do not influence normal age-related cognitive decline. This suggests that physical activity may not reduce normal age-related cognitive decline, and that APOEe4 does not increase normal age-related cognitive decline. However, it is also possible that any detrimental effects of APOEe4 on normal cognitive decline may only be evident for individuals who carry two copies of the e4 allele, or that any previously reported benefits of physical activity may have been attributable to other protective factors that tend to coincide with high levels of physical activity. Future research would benefit from examining the influence of lifetime physical activity on age-related cognitive decline, and from examining whether different types of physical activity have differential effects on age-related cognitive decline.

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Appendix A: Tasmania Human Research Ethics Committee Approval

Dear Ms Padgett,

Ethics Ref: H0016623
Title: Exploring the Roles of Physical Activity and Genetic Predictors on Cognition in Older Adults

This email is to confirm that the following amendment was approved by the Chair of the Tasmania Health and Medical Human Research Ethics Committee on 18/5/2018:

Amendment Newsletter, Email and Mail out invitations
Amendment Accelerometer Instructions
Consent Form PICF PA Amended 110418
Amendment add an additional objective measure of physical activity
Amendment undertake another recruitment drive

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the National Statement on Ethical Conduct in Human Research (NHMRC 2007).

This email constitutes official approval. If your circumstances require a formal letter of amendment approval, please let us know.

Should you have any queries please do not hesitate to contact me.

Kind regards

Lauren Di Palma

--
Executive Officer - Ethics

Appendix B: Participant Information Sheet and Consent Form

Participant Information Sheet [1.2] [11th April 2018]

UNIVERSITY of TASMANIA

PARTICIPANT INFORMATION SHEET

Exploring the Roles of Physical Activity and Genetic Predictors on Cognition in Older Adults

Invitation

We would like to invite you to participate in a research project investigating whether physical activity influences the way genes might impact cognitive function (for example memory and learning). This study is being run as a side-project by researchers in the Tasmanian Healthy Brain Project and researchers at the School of Medicine (Psychology).

The study is being conducted by:

- Dr Christine Padgett, Lecturer in the School of Medicine (Psychology), UTAS
- Associate Professor Mathew Summers, Associate Professor of Neuropsychology and Mental Health, Thompson Institute, USC and Investigator in the Tasmanian Healthy Brain Project, UTAS
- Professor James Vickers, Professor of Pathology, Wicking Centre, UTAS
- Dr Kimberley Stuart, Research Fellow and Project Co-ordinator, The Tasmanian Healthy Brain Project UTAS
- Georgina Conley, 4th year Honours Student in the School of Medicine (Psychology)
- Erin Peavey, Clinical Psychology Masters Student in the School of Medicine (Psychology)

1. **"What is the purpose of this study?"**

   There is evidence that some genes might influence cognitive function in later life (for example, memory and learning). However, it is possible that physical activity influences the effect of these genes. Therefore we would like to investigate the relationship between physical activity, genes thought to influence cognition, and cognition in older adults.

2. **"Why have I been invited to participate in this study?"**

   You have been invited to participate in this study because you are currently participating in the Tasmanian Healthy Brain Project.

3. **"What does this study involve?"**

   For this study, you would be asked to complete two short questionnaires; one asking you about past levels of physical activity and the other asking about your current levels of physical activity. These questionnaires can be either completed online or can be

mailed to your home, where you can complete and the return in a postage-paid envelope that we will provide. Completing the questionnaires should only take about 10 minutes in total. You have a further option of having your physical activity measured using an accelerometer, which is a device that is worn to measure movement. The accelerometer is worn during waking hours for a 7 day period.

We would also ask that we could access the results of the cognitive assessments you have undertaken as part of the Tasmanian Healthy Brain Project, as well as the genetic results from the samples you provided. It is important to note that any data provided by researchers at the Tasmanian Healthy Brain Project would not have your name or any information that could identify who you are. Only Associate Professor Summers or Ms Stuart, who are also researchers on the Tasmanian Healthy Brain Project, would have your identifying information, and would remove these details and insert an alpha-numeric code in its place before passing on as to the current project.

4. "Are there any possible benefits from participating in this study?"

It is not expected that there will be any specific benefits from participating in this study.

5. "Are there any possible risks from participation in this study?"

We do not foresee any risks associated with participating in this study.

6. "What if I have questions about this research?"

If you would like to discuss anything about this study you are very welcome to contact Dr Christine Padgett on 6430 4946 or email her at Christine.Padgett@utas.edu.au. If you have concerns or complaints about the conduct of this study should contact the Executive Officer of the HREC (Tasmania) Network on (03) 6226 7479 or email human.ethics@utas.edu.au. The Executive Officer is the person nominated to receive complaints from research participants. You will need to quote HREC project number H0016623

Thank you for taking the time to consider this study. If you would like to take part, and have received this via email, please click on the link in this email. This will take you to a consent form and then on to the survey. If you have received this via mail, please complete the enclosed consent form and enclosed questionnaires and return using the postage paid envelope.

This information sheet is for you to keep.

UNIVERSITY of TASMANIA

CONSENT FORM

Exploring the Roles of Physical Activity and Genetic Predictors on Cognition in Older Adults

1. I have read and understood the information sheet for this project.
2. I understand that I will be asked questions relating to past and present physical activity, and that this survey will take approximately 10-15 minutes to complete.
3. I understand that I will wear an accelerometer (a device measuring movement), for a period of 7 days. *(Please cross out this point if you do not wish to do this part of the accelerometer study)*
4. I consent that the Tasmanian Healthy Brain Project can release my data to be included in this study.
5. I understand that there are no foreseen risks associated with this study.
6. I understand that all research data will be securely stored at the University of Tasmania for at least five years following publication of results, and will be destroyed when no longer required.
7. Any questions that I have asked have been answered to my satisfaction.
8. I agree that research data gathered from me for the study may be published provided that I cannot be identified as a participant.
9. I understand that any information I provide will be only used for the purposes of this research.
10. I understand that I may withdraw at any time without any consequences, and that I can request for my data to be removed from the study at any time.

If you have read and understood the information sheet and above points, and wish to be involved in the study, please click 'yes' below and you will be directed to the survey. If you do not wish to be part of this study, please click on the 'No' below and you will be exited from the survey. We thank you for your time.

Appendix C: Accelerometer Instructions and Physical Activity Diary

(Participant Code:_____)

Physical Activity Study

Accelerometer Use - Instructions and Diary

Thank you for you willingness to participate in this study. The enclosed accelerometer is designed to be worn during waking hours, so it can be attached each morning and removed each night. We would like you to wear every day it for a full week – so 7 days in a row (it doesn't matter which day of the week you start on). To use the accelerometer, please follow the instructions below. If you have any concerns or questions please either contact either Christine or Kim:

Christine Padgett Phone: 6226 5718
Email: Christine.Padgett@utas.edu.au

Kim Stuart Phone: 6226 4286
Email: Kimberley.Stuart@utas.edu.au

Instructions

1. Each morning, secure the accelerometer around your waist using the supplied band, and adjust to fit firmly, placing it about your **right** leg (see image below).
2. The accelerometer can be worn either over or under clothing, whichever you prefer.
3. Each night, remove the accelerometer before going to bed.
4. Please also complete the diary every day (see overleaf).
5. At the end of the 7 day period, please return the accelerometer and diary using the reply paid envelope provided.

   NOTE: While the accelerometer is water resistant, please remove it for any water activities (showering, swimming etc).

Example of how the ActiGraph Accelerometer is worn.

(From https://www.actigraphcorp.com/actigraph-wgt3x-bt/)

(Participant Code:_____)

7 Day Diary

Please complete this diary for the 7 days you are using the accelerometer. If you forget to use the accelerometer on a given day, please still complete the diary for that day.

Please return this diary with the accelerometer.

Day	Date	Accelerometer worn? (Yes/No)	Did you do any specific activities for exercise? If so, please specify	For how long was each activity done?
Example entry	*1/1/18*	*Y (but took off for shower 9.00am – 9.15 am)*	*1. Walking* *2. Yoga class*	*30 mins* *45 mins*
1				
2				
3				
4				
5				
6				
7				

Thanks again for your time!

Appendix D: Invitation to Participate

Mail-Out Invitation

Dear [name inserted]

Many of you completed the physical activity survey last year, and we would like to say thank you once again to everyone who has participated, we greatly appreciate it!

As you might have seen in the recent newsletter, Dr Christine Padgett is still conducting resesarch investigating the effect of physical activity on later-life cognitive function. So if you have not completed this survey but are interested in doing so, it will simply be a case of completing a short 10 minute questionnaire, either online or by mail. You would also be asked to allow us to use the cognitive assesments and genetic results you have already provided the Tasmanian Healthy Brain Project. All information will be provided to us without any details that could identify you. There is no obligation to be part of this additional study, but we would appreciate your involvement.

We are introducing another tool into the physical activity study. Accelerometers are small devices that are worn during the day, which measure daily activity. We are hoping that people who have previously completed our physical activity survey, or who would like to do so in the coming months, will also be interested in using this additional measure. The details are provided below.

Please note, if you are interested in just completing the survey but not using the accelerometers that is fine. However, to be part of the accelerometer study, you will need to have participated in the physical activity survey.

If you haven't done the physical activity survey yet, but would like to:

Please read the enclosed information sheet, and if you are still willing to participate, it will simply be a case of completing the enclosed questionnaire and consent form. This should take about 10 minutes, and once completed, you can send back in the enclosed pre-paid envelope. If you prefer to do an online version of the survey, please let us know and we can send out an email link.

If you would like to also be included in the accelerometer study:

The accelerometers are worn throughout the day for a 7 day period. They will be mailed to you, along with an instruction sheet and diary to record the accelerometer use. We'll also provide a reply-paid envelope to return them. If you are interested in this part of the study, please contact Dr Christine Padgett (email Christine.Padgett@utas.edu.au, or phone 6226 5718) or Dr Kimberley Stuart at the Tasmanian Healthy Brain Project (email Kimberley.Stuart@utas.edu.au, or phone 6226 4286).

Thank you for your time!

Christine Padgett, on behalf of the research team.

Mail-Out Release 14/05/18